

**REMARKS**

Reconsideration is requested.

Claims 1-29, 32, 34, 35 and 37-40 have been canceled, without prejudice.

Claims 30, 31, 33 and 36 are pending.

The claims define methods of treating retinitis pigmentosa, age-related macular degeneration and/or retinopathy by administering an effective amount of etazolate. One of ordinary skill in the art will appreciate from the present specification that the applicants were in possession of the claimed invention at the time the application was filed. The claimed invention would not have been obvious in view of the art of record. Consideration of the following is requested.

The Section 112, first paragraph "written description", rejection of claims 21-25 and 29 is moot in view of the above amendments. The claims are supported by an adequate written description. The terms and phrases which are understood to be the basis of the rejection are not contained in the pending claims. Withdrawal of the Section 112, first paragraph, rejection is requested.

To the extent not obviated by the above amendments, the Section 103 rejection of claims 21-26, 29-31, 33 and 36 over the combination of Tobinick (WO 01/49321) and Cavalia (Current Medicinal Chemistry 2 (1995) 561-572), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following remarks.

The applicants have demonstrated, in both in vitro and in vivo results, that etazolate exhibits unexpected advantages for treating age-related macular

degeneration, retinitis pigmentosa or retinopathies, as presently claimed. In particular, the inventors have demonstrated, in examples 3-6 of the application, that: etazolate causes a 60% protective effect on cerebellar granular cells in the case of NMDA/serine treatment, and a 57% protective effect in the case of kainate-induced toxicity ; etazolate causes a substantial protective effect cortical neurons and ventral spinal cord cells; etazolate is a PBR ligand which protects neurons from death during excitotoxic phenomena; the photoreceptors of rd1 mice treated with etazolate were better preserved than those of untreated rd-rd mice ; and etazolate was well tolerated upon administration to human subjects and did not cause any side effects. Moreover, the plasma assays confirmed that absorption of the product in humans was good at high doses. Altogether, these results are submitted to demonstrate that etazolate can be used to treat age-related macular degeneration, retinitis pigmentosa or retinopathies, as claimed.

Tobinick relates to the use of TNF antagonists but does not teach the use of etazolate. Cavalia refers to etazolate as having

"been shown to also possess some degree of adenosinergic antagonist activity in addition to inhibition of low  $K_m$  cAMP PDEs" See page 564, left column, penultimate paragraph.

Cavalia does not teach treatment of macular degeneration.

The ability of etazolate to treat macular degeneration would not have been obvious in view of the combination of cited art.

Tobinick relates to proteinaceous TNF antagonists (anti-TNF antibodies or soluble TNF receptor). This document relates to certain types of compounds which are

structurally distinct from etazolate (i.e., protein vs small drug), mechanistically distinct from etazolate (direct binding to TNF while etazolate does not bind TNF), and distinct from etazolate in biological effect (action on inflammatory response caused by TNF vs effect on the cause of ocular degeneration).

No antagonist of Tobinick is reported to have any PDE4 inhibitory activity. Accordingly, the ordinarily skilled person would not have found motivation in the cited art to have combined Tobinick with Cavalla. The claimed invention would not have been reasonably predicted to proceed from a combination of the cited art. Combination of the cited art would not have rendered the claimed invention obvious.

Cavalla provides a general review of the use of PDE4 inhibitors in asthma. There is no indication or suggestion in Cavalla that PDE4 inhibitors can be used in other conditions such as ocular degeneration. Furthermore, there is no disclosure or suggestion in Cavalla that etazolate has the appropriate activity profile for treating ocular degeneration.

The Examiner's rejection is understood to be based on the assumption that modulating TNF is sufficient to conclude that a compound is a candidate for ocular degeneration. The applicants submit, with due respect to the Examiner, that one of ordinary skill would not have viewed the combination of the cited art as suggested by the Examiner.

There is no indication in Cavalla, for example, that etazolate modulates TNF. Furthermore, the inventors have shown, by detailed genetic analyses, that ocular degeneration involves several metabolic pathways, and in particular dys-regulations

within the GABA(A), AKAPA and PDE4 genes (see examples 1 and 2), so that an optimal activity profile for addressing the cause of such diseases implies an effect on these pathways and is not related to TNF.

As stated on page 7, lines 23-27 of the application (emphasis added):

"In a preferred manner, the PDE4 inhibitor compound is also a ligand of the peripheral benzodiazepine receptor (PBR) and the GABA(A) receptor. In fact, said compounds allow to act advantageously on three metabolic pathways involved in neurodegenerative diseases."

The inventors have surprisingly shown that etazolate has the ability to bind the peripheral benzodiazepine receptor (BPR) as well as the GABA(A) receptors.

As described page 34, lines 9-12 of the specification (emphasis added):

"The results show that etazolate induced the same loss of fluorescence as the PBR-specific ligands Ro5-4864 and PK11195. Etazolate therefore appears to be a PBR ligand which protects neurons from death during excitotoxic phenomena."

The disclosure of a TNF inhibitor in Tobinick would not have led the ordinarily skilled person to consider the use of etazolate as presently claimed, considering the structural and mechanistic differences between the compounds. Furthermore, the knowledge in PDE4 inhibition, as mentioned in Cavalla, would not have cured the deficiencies in Tobinick since, for example, the claimed use of etazolate stems inter alia from the discovery, by the inventors, of new properties of etazolate to bind BPR and GABA receptors.

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There was no suggestion in the cited art to have made the claimed invention and withdrawal of the Section 103 rejection of the claims is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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